

Novel Polymer Compounds

This application is a continuation-in-part of U.S. Serial No. 09/256,484, filed
5 February 23, 1999. *pending*

The invention provides compositions comprising a polyanionic polymer, preferably a hydrogel polyanionic polymer, some of which compositions can form a microgel. Polymeric polymers, including polymeric hydrogels, have been developed for medical treatments. Some polymers of the invention, when hydrated, can form either an
10 elastic solid, a viscoelastic solid (like a typical solid gel, for example, a gel like gelatin), a viscoelastic liquid (like a typical gel that can be induced to flow, for example, a gel like petroleum jelly), a viscoelastic liquid that is formed of gel microparticles (such as a Carbopol™ gel) or even a viscous liquid.

Hydrogels are polymeric materials that are highly swollen with water. For many
15 applications, hydrogels are especially useful. Hydrogels are of interest for myriad biomedical applications. These include, but are not limited to, barrier applications (adhesion preventives, sealants), drug delivery devices, tissue engineering and wound healing scaffolds, and materials for cell encapsulation and transplantation:

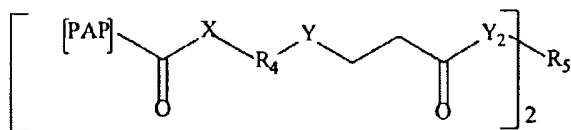
Hydrogels as glues or sealants are desirable to seal leaks in tissues that isolate
20 (gas or liquid phase) fluid-containing cavities. Some examples are blood vessels, the skin, the lung, the blood-brain barrier, and the intestine.

Carbomers are one type of cross-linked hydrogels formed primarily of polyacrylic acid (PAA) based polymers. These gels are formed by free radical polymerization of acrylic acid (AA) in the presence of a multifunctional co-monomer,
25 which thereby serves as a crosslinking agent, for example, (1). These gels can be polymerized under conditions such that microgels form, i.e. small (1-200 μm in the swollen state) cross-linked beads, each bead of which is a cross-linked viscoelastic solid, but the conglomeration of many of which acts like a viscoelastic fluid by virtue of flow of one viscoelastic solid particle over another. The cross-link density and thereby the
30 physical properties of the resulting carbomer microgel can be controlled relatively well by manipulation of the cross-link density, which in turn is controlled by the molar ratio of crosslinking agent to acrylic acid monomer. The physical properties are controlled primarily by the interpretation of chains from the surface of one microgel particle into neighbouring microgel particles and by the elasticity of the microgel particles.

and the reaction conducted over, for example, an 20 or more hours. An example of forming the linked moieties adapted to be reactive in a subsequent free-radical polymerization is reacting with acryloylchloride in dichloromethane in the presence of triethylamine at ambient temperature.

- 5 Other preferred hydrolytically susceptible polymers polyanionic polymers include any in which comprise two or more linearly linked polyanionic segments, where the linkages are through hydrolytically susceptible linking moieties connecting to terminal oxo or thio moieties of the polyanionic segments, such as those described above under Approach IV. Preferably, the segments fall within one or more of the size restraints described here. These linear multimers of
10 polyanionic segments can be further crosslinked with hydrolytically susceptible linking moieties.

- In other preferred hydrolytically susceptible polymers polyanionic polymers, containing carboxylates, for which a sampling of the carboxylate-providing monomers (e.g., 1 of 20) are derivatized to attach $-X-R^4-Y-H$ via an amide, ester or thioester bond, where X and Y are independently S, O or NH and R^4 is a straight chain C_1-C_{10} (preferably C_1-C_5) alkyl which can be
15 substituted with up to two C_1-C_4 alkyls. Preferably, X and Y are different to provide differential reactivities that facilitate selective addition of one end to the polyanionic polymer. However, protecting group chemistry (see illustrations in copending Attorney Docket 314572-103C) can be used to achieve this selective attachment even if X and Y are the same. YH in turn reacts by Michael addition with a crosslinkers (linking moieties) with terminal acrylate or acrylamide
20 moieties. Thus, the linking moiety has the structure:



- , where Y^2 is S, O or NH (preferably O or NH), n is 2 or more (e.g., up to 4, 5 or 6) and R^5 is an hydrolytically susceptible linking moiety comprising C, H and two or more heteroatoms which can be O, S or N, the O, S and N atoms all participating in
25 hydrolytically susceptible bonds or ether or thioether bonds. R^5 can be or include a segment of PAP (such as PEG), which preferably has molecular weight within the above-described preferred ranges. Aside from PAP, which may not be present, R^5 preferably has molecular weight of less than 5,000, more preferably less than 1,000. A large number of examples of R^5 are described herein.

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